DESCRIPTION

3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases mainly caused by abnormal activity of tau protein kinase 1, such as neurodegenerative diseases (e.g. Alzheimer disease).

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and β amyloid protein has been elucidated as their main component (abbreviated as "Aβ" hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated

protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of A β (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, A β abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of A β (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of A β is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of A β are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511

(1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

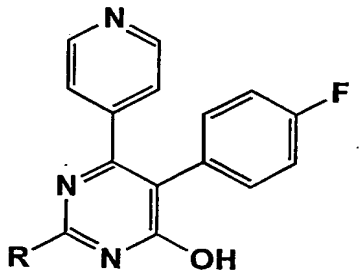
The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic

treatment of neurodegenerative diseases such as cerebrovascular accidents (e.g. ischemic, age-related macular degeneration), Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, Parkinson's disease, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, tauopathies (e.g. Pick's disease, corticobasal degeneration, frontotemporal dementia, progressive supranuclear palsy), and other dementia including vascular dementia; acute and other traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, as well as other diseases such as non-insulin dependent diabetes (such as diabetes type II), obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and several virus-induced tumors.

As structurally similar compounds to the compounds of the present invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



(A)

wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (WO98/24782). The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring and a hydroxy group at the 4-position, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented

by formula (I) are useful as a TPK1 inhibitor or a medicament for therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

Patent Document 1: WO 00/18758

Patent Document 2: WO 01/70728

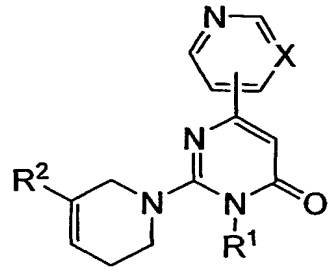
Patent Document 3 WO 01/70729

Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the neurodegenerative diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of A β and the formation of the PHF and by inhibiting the death of nerve cells.

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides 3-substituted-4-pyrimidone derivatives represented by formula (I) or salts thereof, or solvates thereof or hydrates thereof:



(I)

wherein X represents CH or nitrogen atom;

R^1 represents a C_1-C_{12} alkyl group which may be substituted;

R^2 represents a C_1-C_8 alkyl group which may be substituted, a benzene ring which may be substituted, a naphthalene ring which may be substituted, an indan ring which may be substituted, a tetrahydronaphthalene ring which may be substituted, or an optionally substituted heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms in total.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative represented by formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases. As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the disease is selected from the group consisting of Alzheimer disease, cerebrovascular accidents (e.g. ischemic, age-related macular degeneration), Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, Parkinson's disease, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, tauopathies (e.g. Pick's disease,

corticobasal degeneration, frontotemporal dementia, progressive supranuclear palsy), and other dementia including vascular dementia; acute and other traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, as well as other diseases such as non-insulin dependent diabetes (such as diabetes type II), obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and several virus-induced tumors; and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives. The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the salt thereof, and the solvate thereof and the hydrate thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof; and a use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) and the physiologically acceptable salt thereof, and the solvate thereof and the hydrate thereof for the manufacture of the aforementioned medicament.

Best Mode for Carrying Out the Invention

The alkyl group used herein may be either linear or branched. The C_1-C_{12} alkyl group represented by R^1 may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl

group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group or dodecyl group. In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the C_1-C_{12} alkyl group represented by R^1 has one or more substituents, the alkyl group may have one or more substituents selected from the group consisting of a halogen atom; a cyano group; a hydroxyl group; a nitro group; a C_1-C_5 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group; an amino group, C_1-C_3 alkylamino group or C_2-C_6 dialkylamino group; a C_6-C_{10} aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group.

The C_1-C_8 alkyl group represented by R^2 may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group or octyl group.

When the C_1-C_8 alkyl group represented by R^2 has one or more substituents, the alkyl group may have one or more substituents selected from the groups consisting of a halogen atom, a C_1-C_6 alkoxyl group, a C_3-C_8 cycloalkyl group, a benzene ring which may be substituted, a naphthalene ring which may be substituted, phenoxy group which may be substituted or phenylamino group which may be substituted.

When the benzene ring, the naphthalene ring, the phenoxy group, the phenylamino group are substituents of the C_1-C_8 alkyl group represented by R^2, mentioned here above, they may have one or more substituents selected from the group consisting of a C_1-C_5 alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; a C_3-C_6 cycloalkyl

group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; hydroxy group; a C_1-C_5 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C_1-C_5 alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C_1-C_5 halogenated alkyl group such as trifluoromethyl group; hydroxyl group; cyano group; amino group.

When the benzene ring, the naphthalene ring, the indan ring, the tetrahydronaphthalene ring or the heterocyclic ring represented by R^2 has one or more substituents, the rings may have one or more substituents selected from the group consisting of a C_1-C_5 alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group; a C_3-C_6 cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group; a C_3-C_6 cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group; hydroxy group; a C_1-C_5 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C_4-C_7 cycloalkylalkoxyl group such as cyclopropylmethoxy group, cyclopentylmethoxy group; a C_1-C_5 alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C_1-C_5 alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C_1-C_5 halogenated alkyl group such as trifluoromethyl group; a C_1-C_5 halogenated alkoxyl group such as trifluoromethoxy group, 2,2,2-trifluoroethoxy group; cyano group; nitro group; formyl group; a C_2-C_6 alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; a benzene ring, a naphthalene ring, phenoxy group or phenylamino group;

amino group; a C_1-C_5 monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C_2-C_{10} dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; a C_2-C_{10} monoalkylaminomethyl group such as methylaminomethyl group, ethylaminomethyl group, propylaminomethyl group, isoproylaminomethyl group, butylaminomethyl group, isobutylaminomethyl group, tert-butylaminomethyl group, pentylaminomethyl group, isopentylaminomethyl; a C_3-C_{11} dialkylaminomethyl group such as dimethylaminomethyl group, diethylaminomethyl group, ethylmethylaminomethyl group, methylpropylaminomethyl group; pyrrolidinylmethyl group; piperidinylmethyl group; morpholinomethyl group; piperazinylmethyl group; pyrrolylmethyl group; imidazolylmethyl group; pyrazolylmethyl group; triazolylmethyl group; and pyrrolidinylcarbonyl group. The above explained substituents may further be substituted with one or more other substituents which may preferably be chosen from the groups as exemplified above.

The heterocyclic ring having 1 to 4 hetero atoms selected from the group consisting of oxygen atom, sulfur atom, and nitrogen atom, and having 5 to 10 ring-constituting atoms represented by R^2 may be, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, dihydrobenzofuran, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, benzotriazole ring, benzisoxazole ring, 1H-indazole ring, tetrahydroisoquinoline ring, benzothiazolinone ring, benzoxazolinone ring, purine ring, quinolizine ring, quinoline ring, phthalazine

ring, naphthyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, oxadiazole ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, benzodioxole ring, dioxane ring, benzodioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring.

R^1 may preferably be a C_1-C_3 alkyl group, and more preferably a methyl group.

R^2 may preferably be a benzene ring which may be substituted, a thiophene ring which may be substituted, a benzisoxazole ring which may be substituted, a benzyl group which may be substituted, or a phenoxymethyl group which may be substituted.

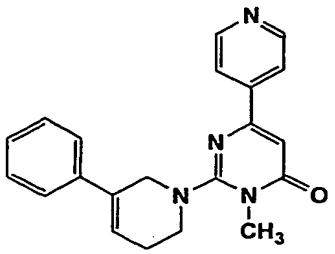
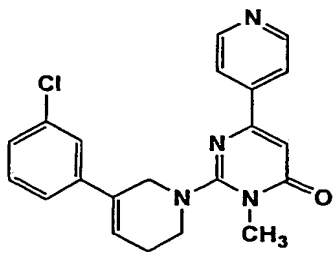
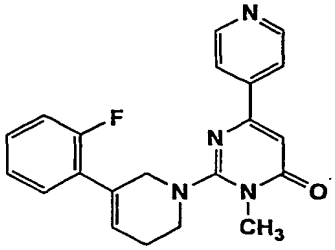
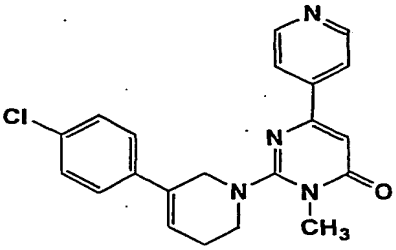
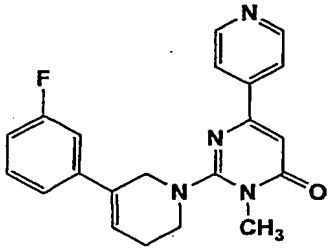
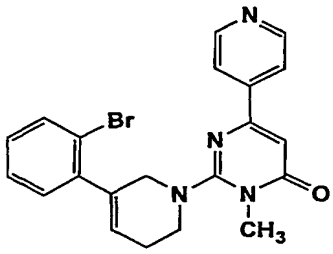
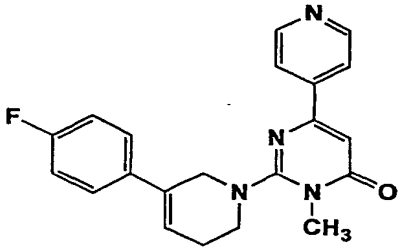
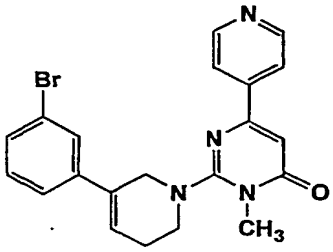
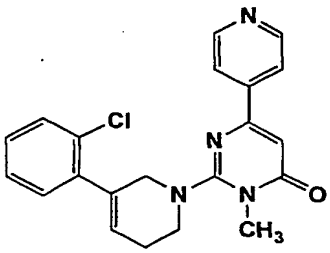
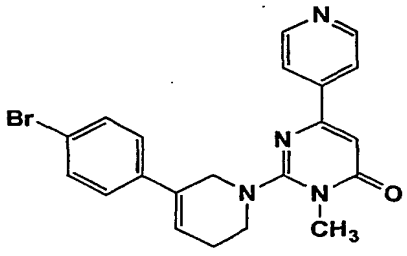
The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

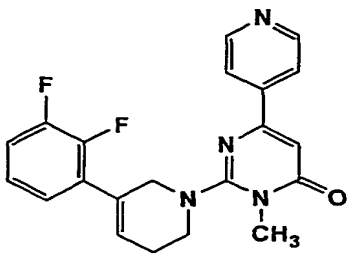
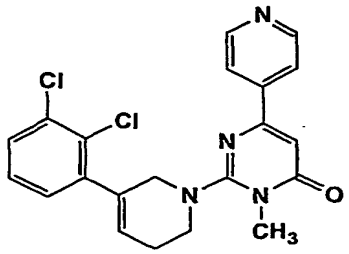
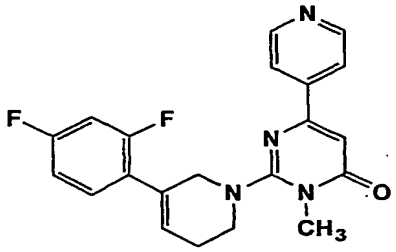
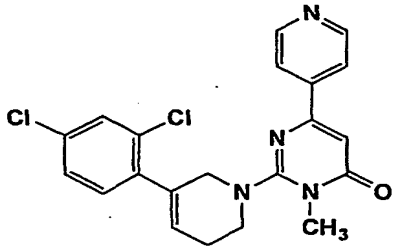
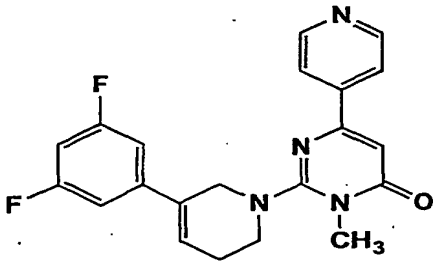
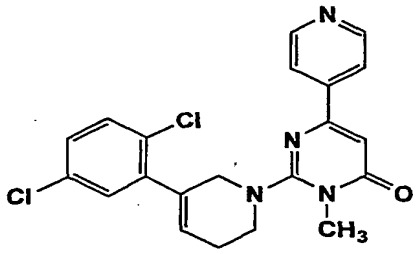
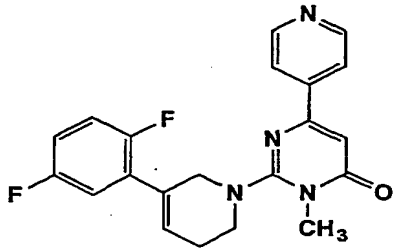
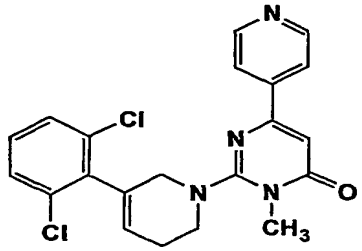
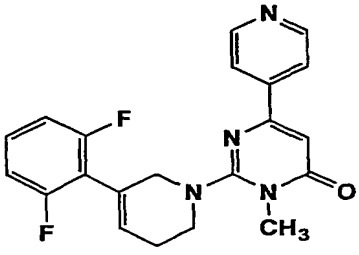
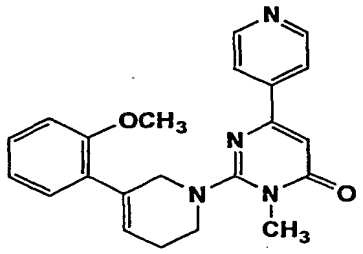
In addition to the 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) may have one or more

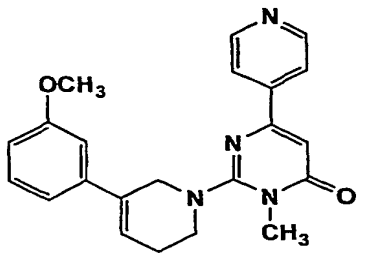
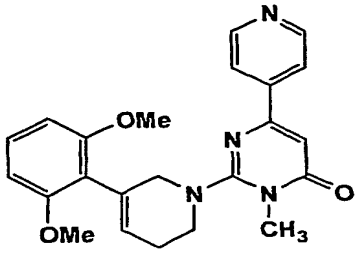
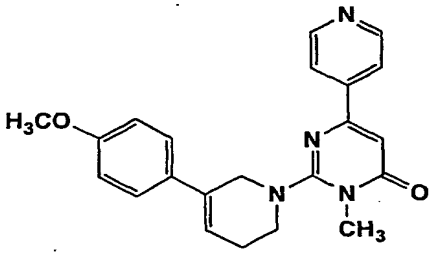
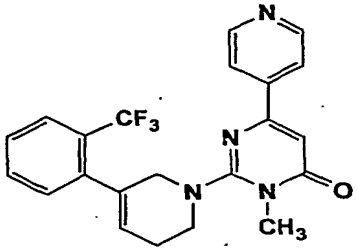
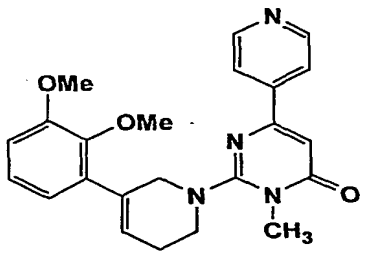
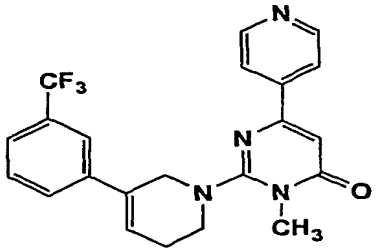
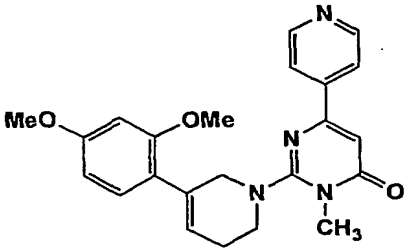
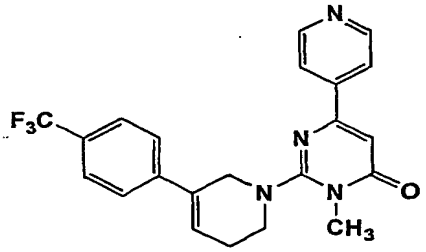
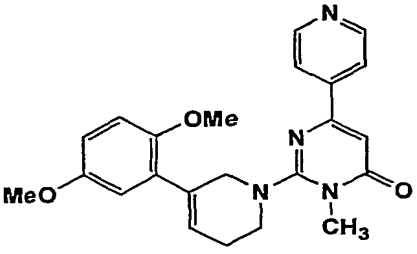
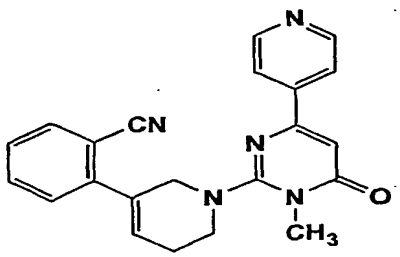
asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention

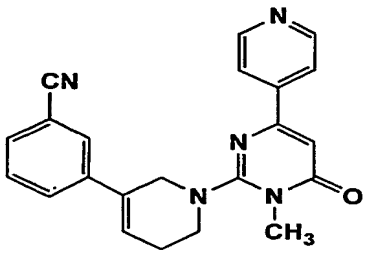
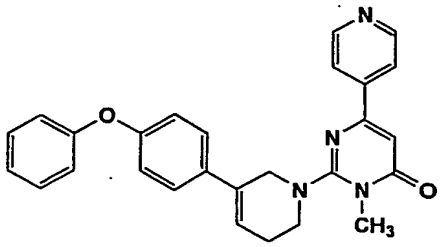
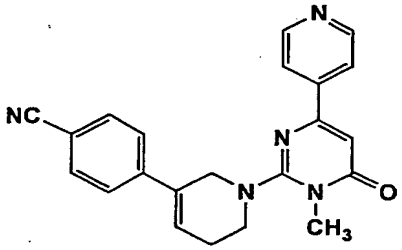
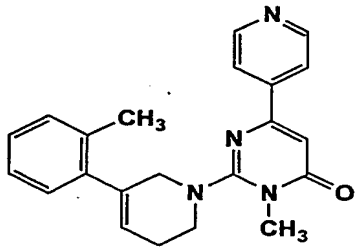
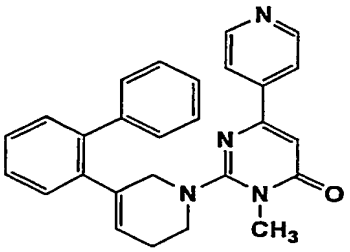
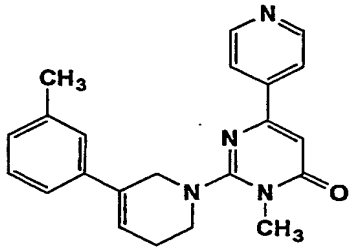
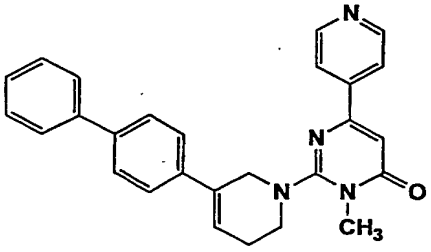
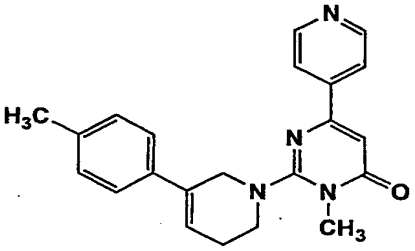
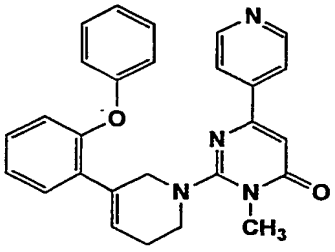
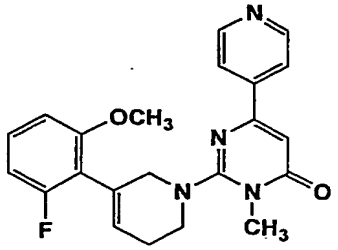
Examples of preferred compounds of the present invention are shown in the table 1 set out below. However, the scope of the present invention is not limited by the following compounds.

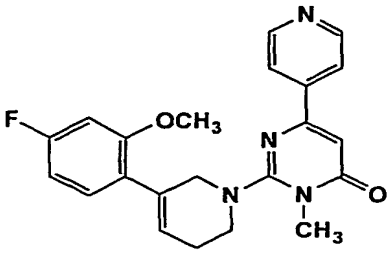
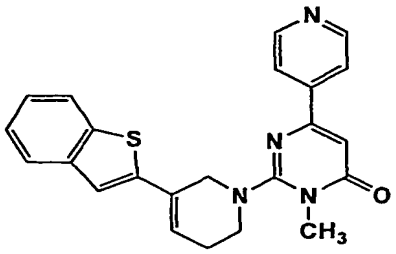
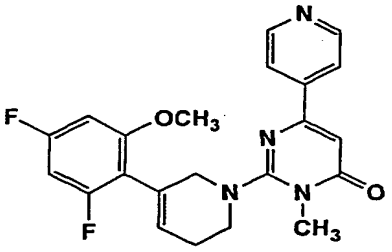
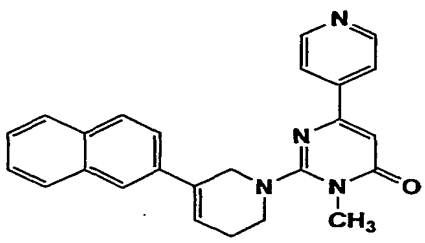
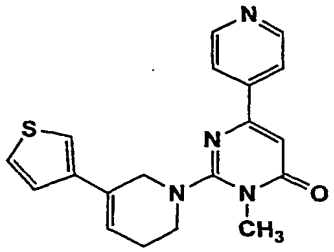
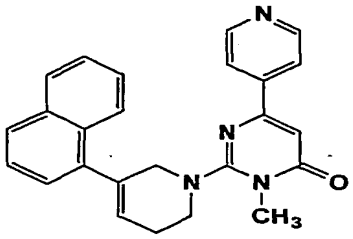
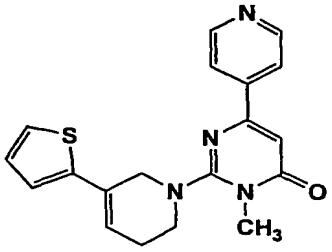
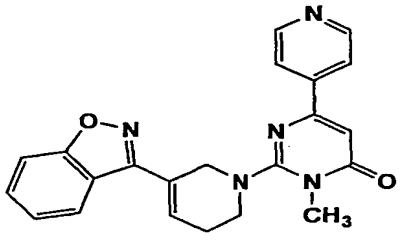
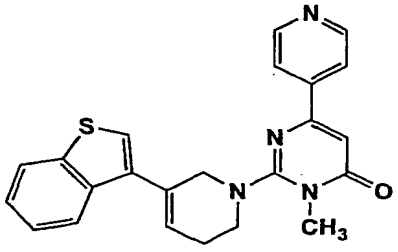
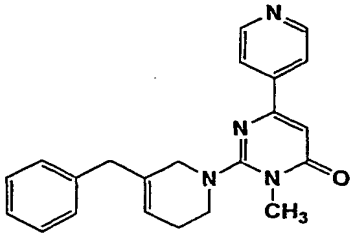
Table 1

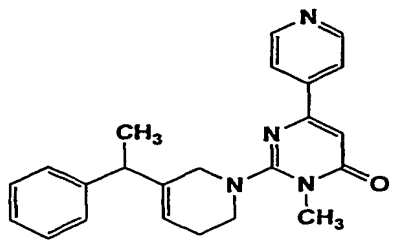
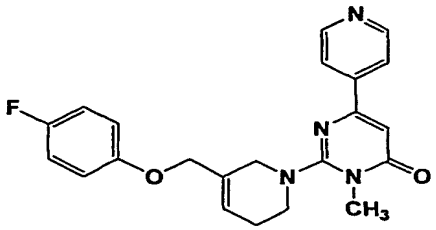
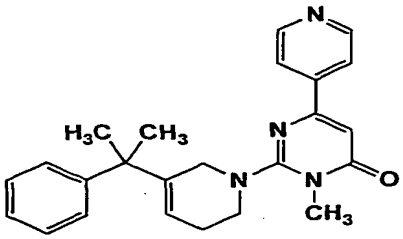
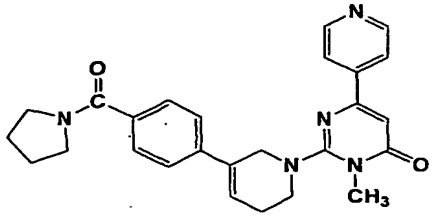
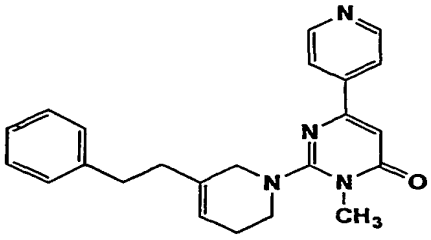
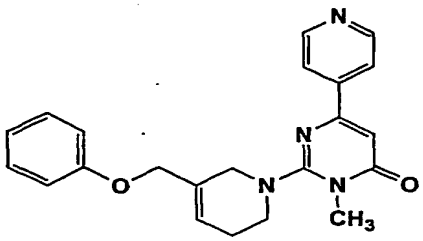
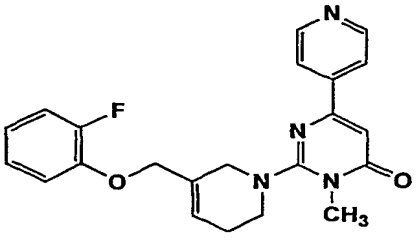
Compound No.	STRUCTURE	Compound No.	STRUCTURE
A001		A006	
A002		A007	
A003		A008	
A004		A009	
A005		A010	

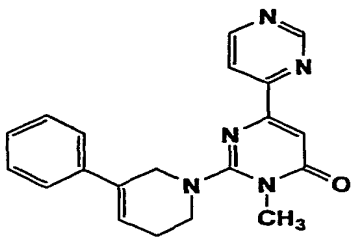
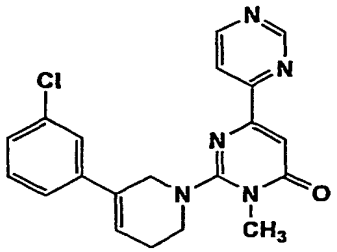
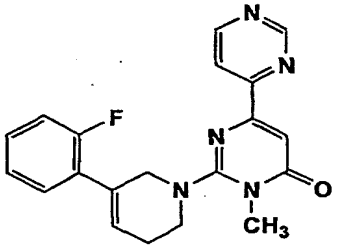
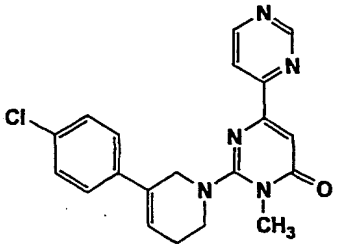
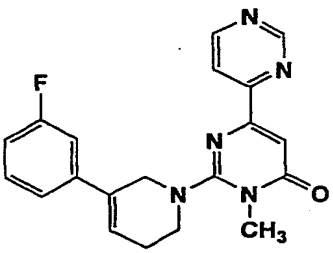
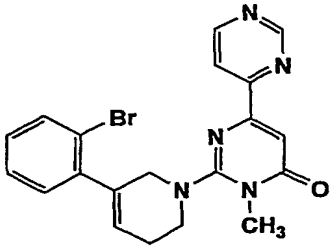
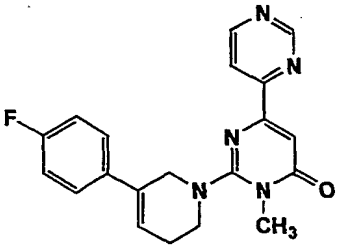
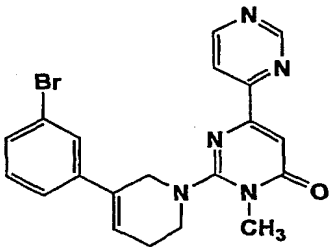
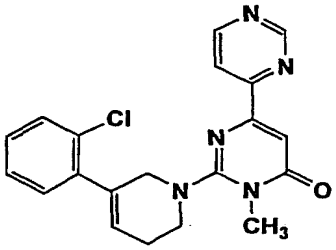
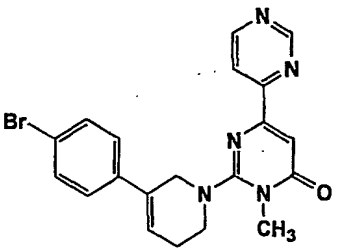
Compound No.	STRUCTURE	Compound No.	STRUCTURE
A011		A016	
A012		A017	
A013		A018	
A014		A019	
A015		A020	

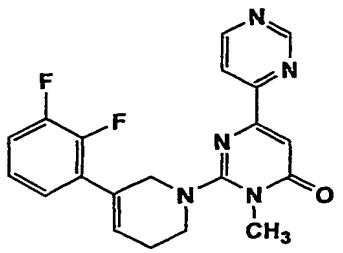
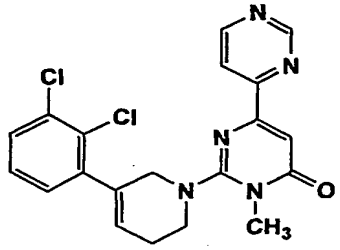
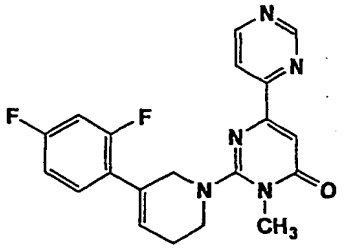
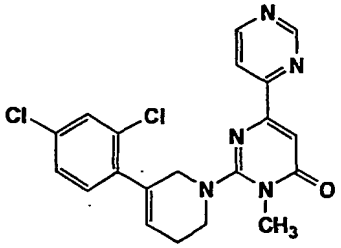
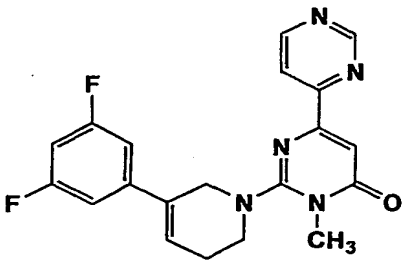
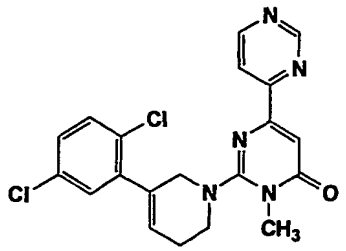
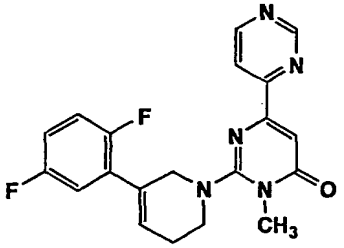
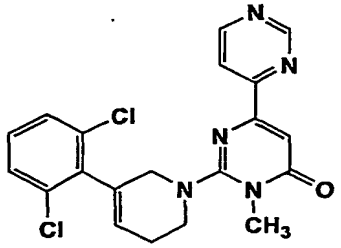
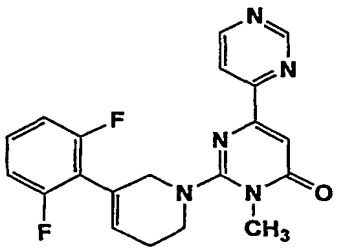
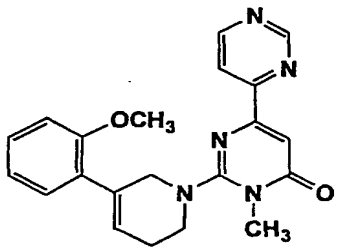
Compound No.	STRUCTURE	Compound No.	STRUCTURE
A021		A026	
A022		A027	
A023		A028	
A024		A029	
A025		A030	

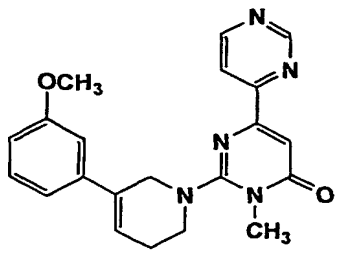
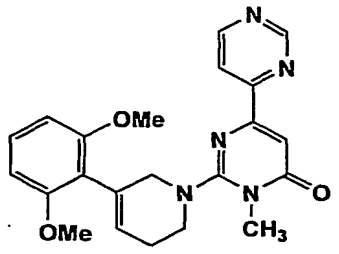
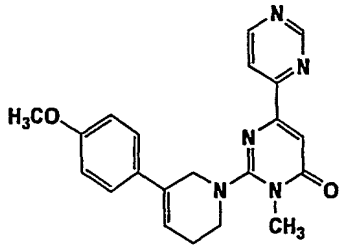
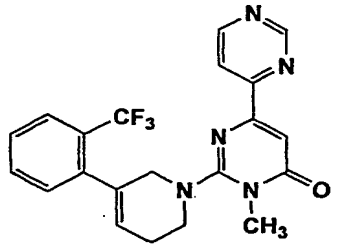
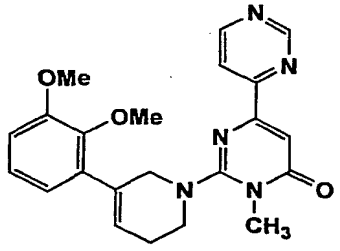
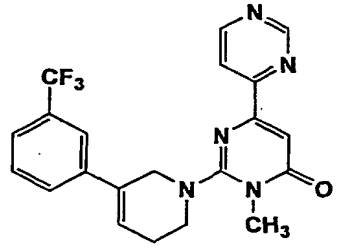
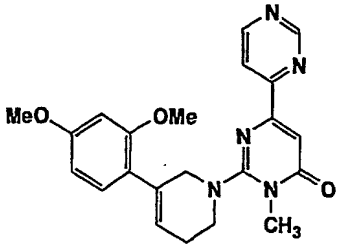
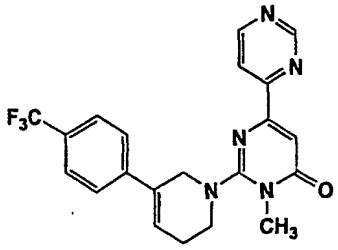
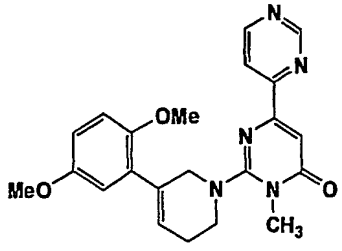
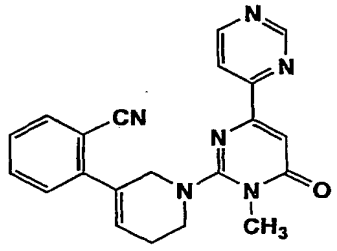
Compound No.	STRUCTURE	Compound No.	STRUCTURE
A031		A036	
A032		A037	
A033		A038	
A034		A039	
A035		A040	

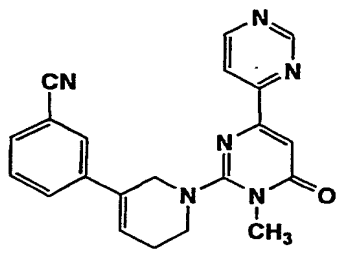
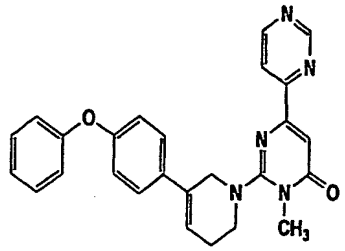
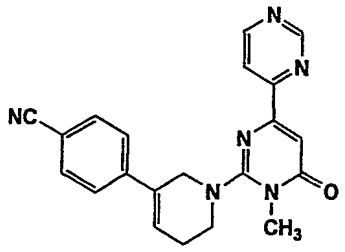
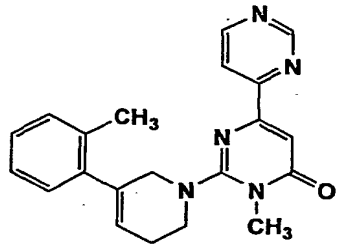
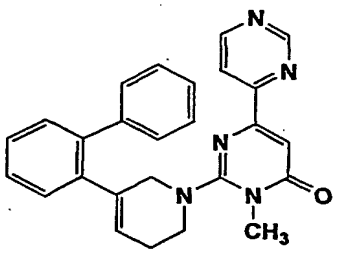
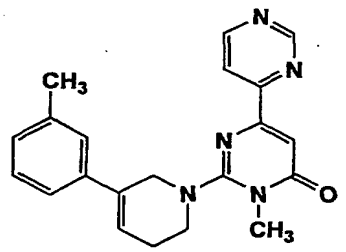
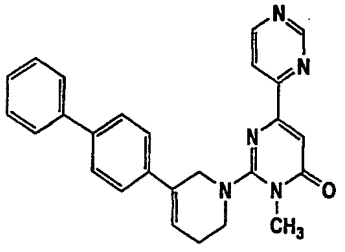
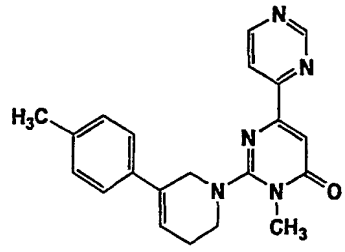
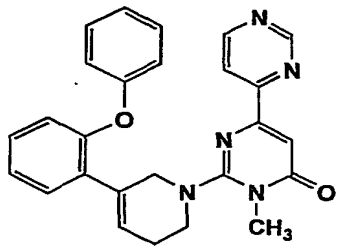
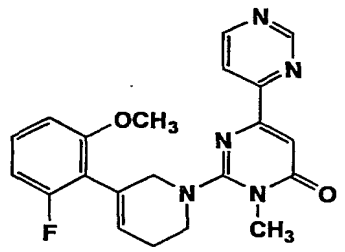
Compound No.	STRUCTURE	Compound No.	STRUCTURE
A041		A046	
A042		A047	
A043		A048	
A044		A049	
A045		A050	

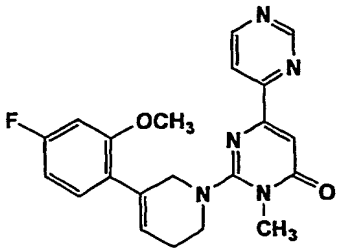
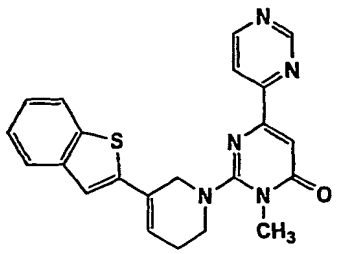
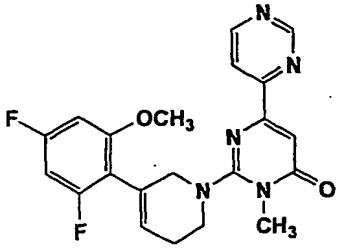
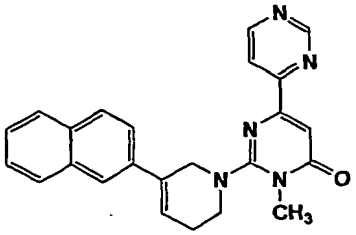
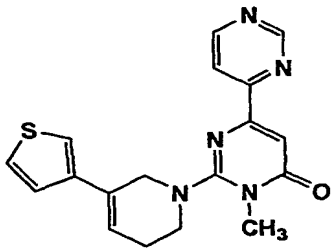
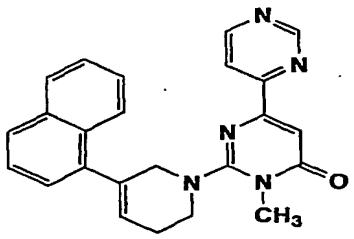
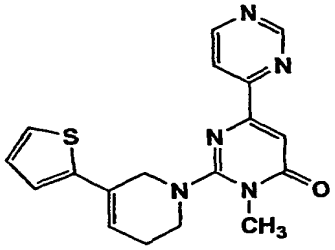
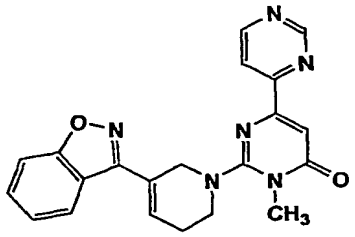
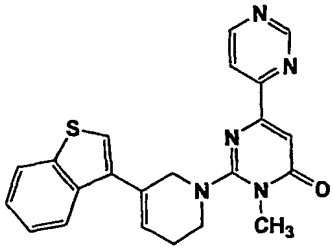
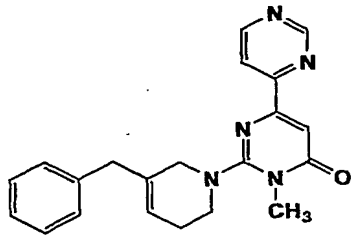
Compound No.	STRUCTURE	Compound No.	STRUCTURE
A051		A056	
A052		A057	
A053		A058	
A054		A059	
A055		A060	

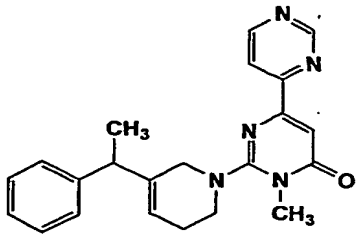
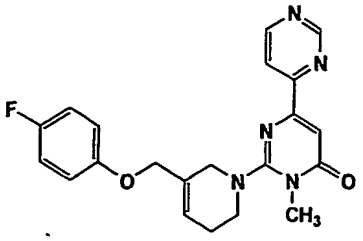
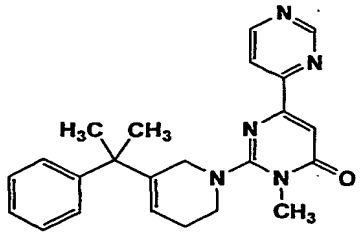
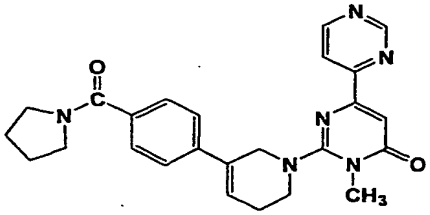
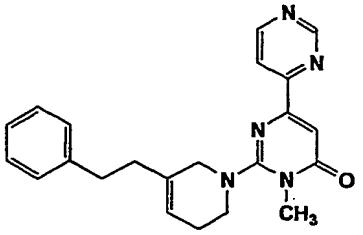
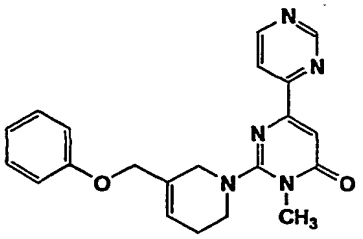
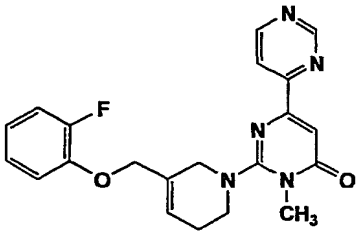
Compound No.	STRUCTURE	Compound No.	STRUCTURE
B001		B006	
B002		B007	
B003		B008	
B004		B009	
B005		B010	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B011		B016	
B012		B017	
B013		B018	
B014		B019	
B015		B020	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B021		B026	
B022		B027	
B023		B028	
B024		B029	
B025		B030	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B031		B036	
B032		B037	
B033		B038	
B034		B039	
B035		B040	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B041		B046	
B042		B047	
B043		B048	
B044		B049	
B045		B050	

Compound No.	STRUCTURE	Compound No.	STRUCTURE
B051		B056	
B052		B057	
B053		B058	
B054		B059	
B055		B060	

Particularly preferred compounds of the present invention represented by formula (I) include:

A001: 2-(5-phenyl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A020: 2-[5-(2-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A022: 2-[5-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A008: 2-[5-(2-bromophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A002: 2-[5-(2-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A004: 2-[5-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A012: 2-[5-(2,4-difluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A005: 2-[5-(2-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A007: 2-[5-(4-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A017: 2-[5-(2,4-dichlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A026: 2-[5-(2,6-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A027: 2-[5-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A049: 2-[5-(benzisoxazole-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one;

A050: 2-(5-benzyl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-

4-one;

A033: 2-(5-biphenyl-2-yl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one;

A043: 2-(5-thiophen-3-yl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one;

A044: 2-(5-thiophen-2-yl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one;

A056: 2-[5-(4-fluorophenoxymethyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one; and

A057: 2-[5-(4-pyrrolidinylcarbonylphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3H-pyrimidin-4-one;

B001: 2-(5-phenyl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B020: 2-[5-(2-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B022: 2-[5-(4-methoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B008: 2-[5-(2-bromophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B002: 2-[5-(2-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B004: 2-[5-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B012: 2-[5-(2,4-difluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B005: 2-[5-(2-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B007: 2-[5-(4-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B017: 2-[5-(2,4-dichlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B026: 2-[5-(2,6-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B027: 2-[5-(2-trifluoromethylphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B049: 2-[5-(benzisoxazole-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B050: 2-(5-benzyl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one;

B033: 2-(5-biphenyl-2-yl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

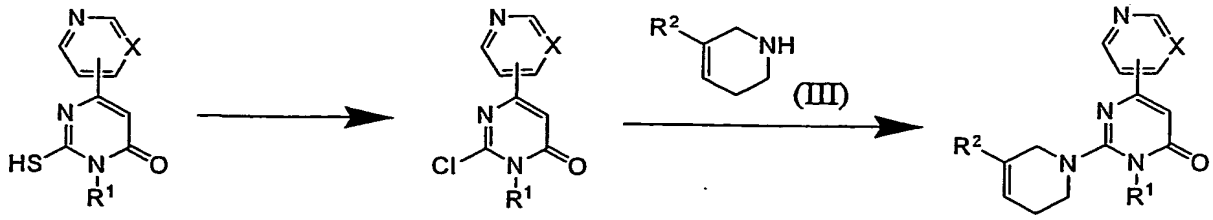
B043: 2-(5-thiophen-3-yl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

B044: 2-(5-thiophen-2-yl-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one;

B056: 2-[5-(4-fluorophenoxymethyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one; and

B057: 2-[5-(4-pyrrolidinylcarbonylphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3H-pyrimidin-4-one. Salts of the aforementioned preferred compound, and solvates or hydrates of the aforementioned compounds and salts thereof are also preferred.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.



(XI) (XII) (I)

(In the above scheme, definitions of R^1 and R^2 are the same as those already described.)

The 2-thiopyrimidone represented by the above formula (XI) is prepared easily by a modification of the method described in EP 354,179. The reaction is carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium t-butoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0℃ to 200℃ under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (XI). Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

Then the 2-thiopyrimidone derivative (XI) is transformed into the 2-chloropyrimidone (XII) by a chlorinating agent. The reaction time and temperature depend on the chlorinating agent used. Examples of a chlorinating agent for the reactions include, for example, thionyl chloride, thionyl chloride and dimethylformamide, phosphorus oxychloride, phosphorus oxychloride and dimethylformamide, oxalyl chloride, phosphorous oxychloride and dimethylformamide,

and phosphorus pentachloride.

The chloride derivative (XII) is then allowed to react with the amine (III) or salts thereof in the presence of a base such as sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, sodium carbonate, sodium hydrogencarbonate, potassium carbonate, triethylamine, diisopropylethylamine, and 1,8-diazabicyclo[5,4,0]undec-7-en for 1 to 100 hours at a suitable temperature ranging from 0 ℃ to 200 ℃ under nitrogen or argon atmosphere or under ordinary air to afford the desired compound (I).

Examples of a solvent for the reactions include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol, ethylene glycol, propylene glycol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide, water and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in neurodegenerative diseases such as Alzheimer disease, thereby suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of cerebrovascular accidents (e.g. ischemic, age-related macular degeneration), Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, Parkinson's disease, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, tauopathies (e.g. Pick's disease,

corticobasal degeneration, frontotemporal dementia, progressive supranuclear palsy), and other dementia including vascular dementia; acute and other traumatic injuries, brain and spinal cord trauma, peripheral neuropathies, retinopathies and glaucoma, as well as other diseases such as non-insulin dependent diabetes (such as diabetes type II), obesity, manic depressive illness, schizophrenia, alopecia, cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia, and a virus-induced tumor.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the like.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as

physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content rations of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the

medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Reference example 1:

Synthesis of 2-mercapto-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one

A solution of ethyl 3-oxo-3-(4-pyridyl)propionate (29.0 g, 150 mmol), N-methyl thiourea (40.6 g, 450 mmol) and 1,8-diazabicyclo[5,4,0]-7-undecene (22.4 ml, 150 mmol) was refluxed for 4 hours and the solution of methanesulfonic acid (14.4 g, 150 mmol) in water (50 ml) was added after cooling by ice-water. The precipitate was washed with water, filtered and dried to give the title compound (23.7 g, 72%).
^{1}H-NMR (DMSO-d_6) δ : 3.58(s, 3H), 6.40(s, 1H), 7.72(dd, J=1.8, 4.5Hz, 2H), 8.73(dd, J=1.5, 4.8Hz, 2H), 12.92(brd, 1H).

Reference example 2:

Synthesis of 2-chloro-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one

Phosphorous oxychloride (26.11g, 170 mmol) was added to dimethylformamide(180 ml) and stirred 20 min.
2-mercapto-3-methyl-6-(4-pyridyl)-pyrimidine-4-one (24.15 g, 110 mmol) was added to the solution and stirred 5 min and then stirred at 70℃ for 2 hours. Ethyl acetate (630 ml) was added to the ice-cooled solution and precipitate was collected by filtration after 20 minutes stirring. After drying, the precipitate was dissolved in water (400 ml) and pH was adjusted to 10 by aqueous sodium hydroxide. The precipitate was washed with

water, filtered and dried to give the title compound (18.82 g, 77%).

^{1}H-NMR ($CDCl_3$) δ : 3.72(s, 3H), 6.90(s, 1H), 7.78(dd, J=1.7, 4.5Hz, 2H), 8.75(dd, J=1.6, 4.5Hz, 2H).

Reference example 3:

Synthesis of 2-mercapto-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one

A solution of ethyl 3-oxo-3-(4-pyrimidyl)propionate (34.1 g, 176 mmol), N-methylthiourea (47.5 g, 527 mmol) and 1,8-diazabicyclo[5,4,0]-7-undecene (26.3 ml, 176 mmol) in ethanol(340ml) was refluxed for 2 hours and the solution of methanesulfonic acid (16.9 g, 176 mmol) in water (70 ml) was added after cooling by ice-water. The precipitate was washed with water, filtered and dried to give the title compound (30.2 g, 78%).

^{1}H-NMR (DMSO-d_6) δ : 3.56(s, 3H), 6.88(s, 1H), 8.24(dd, J=1.2, 5.4Hz, 1H), 9.05(d, J=5.4Hz, 1H), 9.38(s, 1H), 11.94(s, 1H).

MS[M-H]$^-$: 219.

Reference example 4:

Synthesis of 2-chloro-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one

Phosphorous oxychloride (4.60g, 30 mmol) was added to dimethylformamide(32 ml) and stirred 20 min at 0℃. 2-Mercapto-3-methyl-6-pyrimidin-4-yl-pyrimidin-4-one (4.40 g, 20 mmol) was added to the solution and stirred 5 min and then stirred at 70℃ for 1 hour. The reaction mixture was poured into ice water, neutralized by solid K_2CO_3, and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. Purification of the residue by silica gel column chromatography (ethyl acetate) gave the title compound (1.20 g, 27%).

^{1}H-NMR ($CDCl_3$) δ : 3.74(s, 3H), 7.56(s, 1H), 8.18 (d, J=5.1, 1H), 8.92 (d, J=5.1Hz, 1H), 9.30(s, 1H).

MS[M$^+$H]$^+$: 223.

Example 1: Synthesis of 2-[5-(2-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one: {3-methyl-2-[5-(2-chlorophenyl)-3,6-dihydropyridin-1(2H)-yl]-6-pyridin-4-ylpyrimidin-4(3*H*)-one} (Compound No.A005 in Table-1)

A mixture of 2-chlorophenylboronic acid (5.0 g), 3-bromopyridine (4.8 g) and tetrakis(triphenylphosphine)palladium(0) (1.0 g) in toluene (47 ml), aqueous 2 M sodium carbonate solution (35 ml) and ethanol (2.4 ml) was heated under reflux for 5.5 h. The reaction mixture was cooled, and the toluene layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate evaporated under reduced pressure to give crude 3-(2-chlorophenyl)pyridine (7.9 g). To a solution of the 3-(2-chlorophenyl)-pyridine (7.9 g) in dichloromethane (50 ml) was added iodomethane (3.8 ml) and the mixture was stirred for 15 h. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate to give a pale-yellow crystal. To a solution of the obtained crystals in methanol (60 ml) was added sodium borohydride (1.7 g) under ice-cooling, and the mixture was stirred at room temperature for 3 h. The mixture was quenched with a saturated aqueous sodium solution. The mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude 5-(2-chlorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine (5.9 g).

To a solution of the 5-(2-chlorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine (5.9 g) in dichloromethane (60 ml) was added 1-chloroethyl chloroformate (5.1 ml) and the mixture was stirred for 2.5 h. The mixture was washed with water and then with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give brown oil. A solution of the obtained oil in methanol was refluxed for 2 h. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from

ethyl acetate to give 5-(2-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (2.4 g). A solution of 5-(2-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (156 mg), 2-chloro-1,6-dihydro-1-methyl-6-oxo-4-(pyridin-4-yl)pyrimidine (150 mg) and triethylamine (236 μl) in dimethylformamide (3 ml) was stirred at room temperature for 6 h. To the reaction mixture was added water (3 ml), and the precipitated crystals were collected by filtration to give the title compound (240 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ : 2.56(m, 2H), 3.53(m, 2H), 3.55(s, 3H), 4.10(s, 2H), 5.88(m, 1H), 6.65(s, 1H), 7.20-7.27(m, 3H), 7.39(m, 1H), 7.83(d, J = 5.2 Hz, 2H), 8.67(d, J = 5.2 Hz, 2H)

MS: 378(M+)

Example 2: Synthesis of 2-[5-(2,6-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyridin-4-yl-3*H*-pyrimidin-4-one: {3-methyl-2-[5-(2,6-dimethoxyphenyl)-3,6-dihydropyridin-1(2H)-yl]-6-pyridin-4-ylpyrimidin-4(3*H*)-one} (Compound No.A026 in Table-1)

5-(2,6-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrochloride was prepared from 2,6-dimethoxyphenylboronic acid in the same manner as in Example 1. A solution of 5-(2,6-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (173 mg), 2-chloro-1,6-dihydro-1-methyl-6-oxo-4-(pyridin-4-yl)pyrimidine (150 mg) and triethylamine (236 μ l) in dimethylformamide (5 ml) was stirred at room temperature for 2 h. To the reaction mixture was added water (5 ml), and the precipitated crystals were collected by filtration to give the title compound (250 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ : 2.57(m, 2H), 3.53(s, 3H), 3.58(m, 2H), 3.75(s, 6H), 3.93(m, 2H), 5.74(m, 1H), 6.55-6.61(m, 3H), 7.21(m, 1H), 7.81(d, J = 6.4 Hz, 2H), 8.67(d, J = 6.0 Hz, 2H)

MS: 404(M+)

Example 3: Synthesis of 2-[5-(2-chlorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-

6-pyrimidin-4-yl-3*H*-pyrimidin-4-one: {3-methyl-2-[5-(2-chlorophenyl)-3,6-dihydropyridin-1(2H)-yl]-6-pyrimidin-4-ylpyrimidin-4(3*H*)-one} (Compound No.B005 in Table-1)

A mixture of 2-chlorophenylboronic acid (5.0 g), 3-bromopyridine (4.8 g) and tetrakis(triphenylphosphine)palladium(0) (1.0 g) in toluene (47 ml), aqueous 2 M sodium carbonate solution (35 ml) and ethanol (2.4 ml) was heated under reflux for 5.5 h. The reaction mixture was cooled, and the toluene layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate evaporated under reduced pressure to give crude 3-(2-chlorophenyl)pyridine (7.9 g). To a solution of the 3-(2-chlorophenyl)pyridine (7.9 g) in dichloromethane (50 ml) was added iodomethane (3.8 ml) and the mixture was stirred for 15 h. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate to give a pale-yellow crystal. To a solution of the obtained crystals in methanol (60 ml) was added sodium borohydride (1.7 g) under ice-cooling, and the mixture was stirred at room temperature for 3 h. The mixture was quenched with a saturated aqueous sodium solution. The mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give a crude 5-(2-chlorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine (5.9 g).

To a solution of the 5-(2-chlorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine (5.9 g) in dichloromethane (60 ml) was added 1-chloroethyl chloroformate (5.1 ml) and the mixture was stirred for 2.5 h. The mixture was washed with water and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to give brown oil. A solution of the obtained oil in methanol was refluxed for 2 h. The solvent was evaporated under reduced pressure and the obtained residue was crystallized from ethyl acetate to give 5-(2-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (2.4 g). A solution of 5-(2-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (155

mg), 2-chloro-1,6-dihydro-1-methyl-6-oxo-4-(pyridin-4-yl)pyrimidine (150 mg) and triethylamine (235 μl) in dimethylformamide (3 ml) was stirred at room temperature for 2 h. To the reaction mixture was added water (3 ml), and the precipitated crystals were collected by filtration to give the title compound (240 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ : 2.56(m, 2H), 3.52(m, 2H), 3.56(s, 3H), 4.09(m, 2H), 5.88(m, 1H), 7.21-7.29(m, 4H), 7.39(m, 1H), 8.13(d, *J* = 5.1 Hz, 1H), 8.82(d, *J* = 5.1 Hz, 1H), 9.25(s, 1H)

MS: 379(M+)

Example 4: Synthesis of 2-[5-(2,6-dimethoxyphenyl)-3,6-dihydro-2H-pyridin-1-yl]-3-methyl-6-pyrimidin-4-yl-3*H*-pyrimidin-4-one: {3-methyl-2-[5-(2,6-dimethoxyphenyl)-3,6-dihydropyridin-1(2H)-yl]-6- pyrimidin-4-ylpyrimidin-4(3*H*)-one} (Compound No.B026 in Table-1)

5-(2,6-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrochloride was prepared from 2,6-dimethoxyphenylboronic acid in the same manner as in Example 1. A solution of 5-(2,6-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (172 mg), 2-chloro-1,6-dihydro-1-methyl-6-oxo-4-(pyridin-4-yl)pyrimidine (150 mg) and triethylamine (235 μ l) in dimethylformamide (6 ml) was stirred at room temperature for 3 h. To the reaction mixture was added water (10 ml), and the precipitated crystals were collected by filtration to give the title compound (260 mg) as white crystals.

^{1}H-NMR ($CDCl_3$) δ : 2.60(m, 2H), 3.57-3.61(m, 5H), 3.78(s, 6H), 3.94(m, 2H), 5.76(m, 1H), 6.59(d, *J* = 8.5 Hz, 2H), 7.22-7.28(m, 2H), 8.20(d, *J* = 5.4 Hz, 1H), 8.84(d, *J* = 5.4 Hz, 1H), 9.27(s, 1H)

MS: 405(M+)

The compounds in the following table 2 were prepared in the same manner as the methods described above. The compound numbers in the following table correspond to those shown in the above-described table 1 of preferred compounds.

Table 2

Compound No.	^{1}H-NMR (Solvent) δ :	[M+H]+
A001	($CDCl_3$) 2.57(m, 2H), 3.50(m, 2H), 3.59(s, 3H), 4.26(m, 2H), 6.25(m, 1H), 6.68(s, 1H), 7.32-7.40(m, 5H), 7.82(d, J = 6.0 Hz, 2H), 8.72(d, J = 6.0 Hz, 2H)	345
A002	(d_6-DMSO) 2.4-2.6(m,2H), 3.44(s, 3H), 3.51(m, 2H), 4.19(s, 2H), 6.14(bs, 1H), 6.82(s, 1H), 7.20-7.30(m, 2H), 7.31-7.50(m, 2H), 7.97(d, J = 5.4 Hz, 2H), 8.68(d, J = 5.4 Hz, 2H)	363
A004	($CDCl_3$) 3.19(m, 2H), 3.63(s, 3H), 3.78(m, 2H), 4.55(s, 2H), 6.68(s, 1H), 7.25-7.31(m, 3H), 7.47(m, 2H), 7.82(d, J = 6.0 Hz, 2H), 8.74(d, J = 6.0 Hz, 2H)	363
A005	($CDCl_3$) 2.56(m, 2H), 3.53(m, 2H), 3.55(s, 3H), 4.10(s, 2H), 5.88(m, 1H), 6.65(s, 1H), 7.20-7.27(m, 3H), 7.39(m, 1H), 7.83(d, J = 5.2 Hz, 2H), 8.67(d, J = 5.2 Hz, 2H)	378(M+)
A008	($CDCl_3$) 2.56(m, 2H), 3.52-3.56(m, 5H), 4.08(s, 2H), 5.85(m, 1H), 6.65(s, 1H), 7.16-7.32(m, 3H), 7.57(d, J = 8.0 Hz, 1H), 7.83(m, 2H), 8.68(m, 2H)	424
A012	($CDCl_3$) 2.55(m, 2H), 3.51(m, 2H), 3.55(s, 3H), 4.14(s, 2H), 6.05(m, 1H), 6.66(s, 1H), 6.80-6.89(m, 2H), 7.21-7.27(m, 2H), 7.84(d, J = 6.1 Hz, 2H), 8.69(d, J = 6.1 Hz, 2H)	380(M+)

A017	($CDCl_3$) 2.55(m, 2H), 3.50-3.58(m, 5H), 4.06(m, 2H), 5.88(m, 1H), 6.65(s, 1H), 7.15(d, J = 8.3 Hz, 1H), 7.22-7.27(m, 1H), 7.41(d, J = 2.0 Hz, 1H), 7.83(m, 2H), 8.68(d, J = 5.8 Hz, 2H)	414
A020	($CDCl_3$) 2.57(m, 2H), 3.57(s, 3H), 3.58(m, 2H), 3.82(s, 3H), 4.18(m, 2H), 5.92(m, 1H), 6.65(s, 1H), 6.89-6.98(m, 2H), 7.19(m, 1H), 7.30(m, 1H), 7.81 (d, J = 6.0 Hz, 2H), 8.69(d, J = 6.0 Hz, 2H)	375
A022	(d_6-DMSO) 2.4-2.6(m,2H), 3.47(s, 3H), 3.77(m, 2H), 4.26(s, 2H), 6.23(bs, 1H), 7.02(s, 1H), 6.94, 7.44(ABq, 4H, J = 8.7 Hz), 8.44 (d, J = 5.4 Hz, 2H), 8.91(d, J = 5.4 Hz, 2H)	375
A026	($CDCl_3$) 2.57(m, 2H), 3.53(s, 3H), 3.58(m, 2H), 3.75(s, 6H), 3.93(m, 2H), 5.74(m, 1H), 6.55-6.61(m, 3H), 7.21(m, 1H), 7.81 (d, J = 6.4 Hz, 2H), 8.67(d, J = 6.0 Hz, 2H)	404(M+)
A027	($CDCl_3$) 2.53(m, 2H), 3.50(m, 2H), 3.54(s, 3H), 4.01(m, 2H), 5.82(m, 1H), 6.65(s, 1H), 7.29(d, J = 7.6 Hz, 1H), 7.42(m, 1H), 7.52(m, 1H), 7.68(d, J = 7.8 Hz, 1H), 7.83(d, J = 6.1 Hz, 2H), 8.67(d, J = 6.1 Hz, 2H)	412(M+)
A033	($CDCl_3$) 2.57(m, 2H), 3.02(s, 3H), 3.46-3.49(m, 4H), 6.00(m, 1H), 6.58(s, 1H), 7.22-7.38(m, 9H), 7.80(d, J = 6.1 Hz, 2H), 8.71(d, J = 6.1 Hz, 2H)	420(M+)
A043	($CDCl_3$) 2.55(m, 2H), 3.47(m, 2H), 3.56(s, 3H), 4.22(m, 2H), 6.28(m, 1H), 6.67(s, 1H), 7.16(d, J = 1.7 Hz, 1H), 7.17-7.27(m, 2H),	350(M+)

	7.33(dd, J = 2.9, 5.1 Hz, 1H), 7.89(dd, J = 1.5, 4.6 Hz, 2H), 8.71(d, J = 6.1 Hz, 2H),	
A044	($CDCl_3$) 2.54(m, 2H), 3.47(m, 2H), 3.56(s, 3H), 4.24(m, 2H), 6.29(m, 1H), 6.67(s, 1H), 7.00-7.02(m, 2H), 7.19(m, 1H), 7.85(dd, J = 1.7, 4.6 Hz, 2H), 8.70(d, J = 6.1 Hz, 2H),	350(M+)
A049	(d_6-DMSO) 2.67(m,2H), 3.45(s, 3H), 3.55(m, 2H), 4.42(s, 2H), 6.82(s, 1H), 7.13(s, 1H), 7.44(m, 1H), 7.68(m, 1H), 7.79(d, J = 7.8 Hz, 1H), 7.97(d, J = 5.4 Hz, 2H), 8.16(d, J = 7.8 Hz, 1H), 8.67(d, J = 5.4 Hz, 2H)	385(M+)
A050	($CDCl_3$) 2.40(bs, 2H), 3.31-3.49(m, 4H), 3.41(s, 3H), 3.72(d, J = 1.5 Hz, 2H), 5.68(bs, 1H), 6.62(s, 1H), 7.18-7.38(m, 5H), 7.77(d, J = 6.0 Hz), 8.70 (d, J = 6.0 Hz)	359
A056	(d_6-DMSO) 2.39(bs, 2H), 3.2-3.5(m, 2H), 3.35(s, 3H), 3.98(bs, 2H), 4.54(s, 2H), 6.05(bs, 1H), 6.9-7.2(m, 4H), 8.44(d, J = 6.5 Hz), 8.93(d, J = 6.5 Hz)	393
A057	($CDCl_3$) 1.80-2.10(4H,m), 2.50-2.65(2H,m), 3.48(4H,dd,J=6.3,14.1Hz), 3.59(3H,m), 3.66(2H,t,J=6.6Hz), 4.26(2H,d,J=1.8Hz), 6.25-6.35(1H,m), 6.68(1H,s), 7.43(2H,d,J=8.4Hz), 7.55(2H,d,J=8.4Hz), 7.82(2H,dd,J=1.5,4.8Hz), 8.72(2H,dd,J=1.5,4.5Hz)	442

Compound No.	^{1}H-NMR (Solvent) δ :	[M+H]+
B001	($CDCl_3$) 2.55(m, 2H), 3.46(m, 2H), 3.57(s, 3H), 4.24(m, 2H), 6.22(m, 1H), 7.24-7.40(m, 6H), 8.15(d, J = 5.1 Hz, 1H), 8.85(d, J = 5.1 Hz, 1H), 9.26(s, 1H)	346
B002	($CDCl_3$) 2.55(m, 2H), 3.51(m, 2H), 3.56(s, 3H), 4.18(m, 2H), 6.08(m, 1H), 7.05-7.15(m, 2H), 7.24-7.30(m, 3H), 8.15(d, J = 5.1 Hz, 1H), 8.83(d, J = 5.1 Hz, 1H), 9.25(s, 1H)	363(M+)
B004	(d_6-DMSO) 2.48-2.50(m, 2H), 3.46-3.47(m, 5H), 4.25(m, 2H), 6.30(m, 1H), 6.98(s, 1H), 7.20(m, 2H), 7.55(m, 2H), 8.26(d, J = 5.1 Hz, 1H), 8.99(d, J = 5.1 Hz, 1H), 9.28(d, J = 1.5 Hz, 1H)	363(M+)
B005	($CDCl_3$) 2.56(m, 2H), 3.52(m, 2H), 3.56(s, 3H), 4.09(m, 2H), 5.88(m, 1H), 7.21-7.29(m, 4H), 7.39(m, 1H), 8.13(d, J = 5.1 Hz, 1H), 8.82(d, J = 5.1 Hz, 1H), 9.25(s, 1H)	379(M+)
B008	($CDCl_3$) 2.52(m, 2H), 3.48(m, 2H), 3.52(s, 3H), 4.03(m, 2H), 5.81(m, 1H), 7.11-7.28(m, 4H), 7.54(d, J = 8.0 Hz, 1H), 8.11(d, J = 5.1 Hz, 1H), 8.78(d, J = 5.1 Hz, 1H), 9.21(s, 1H)	425
B012	(d_6-DMSO) 2.48-2.50(m, 2H), 3.44(s, 3H), 3.50(m, 2H), 4.17(m, 2H), 6.11(m, 1H), 6.97(s, 1H), 7.11(m, 1H), 7.28(m, 1H), 7.49(m, 1H), 8.19(d, J = 5.1 Hz, 1H), 8.97(d, J = 5.1 Hz, 1H), 9.28(s, 1H)	381(M+)

B017	($CDCl_3$) 2.55(m, 2H), 3.49(m, 2H), 3.55(s, 3H), 4.05(m, 2H), 5.88(m, 1H), 7.16(d, J = 8.5 Hz, 1H), 7.23-7.25(m, 1H), 7.29(s, 1H), 8.12(d, J = 5.1 Hz, 1H), 8.82(d, J = 5.1 Hz, 1H), 9.25(s, 1H)	415
B022	($CDCl_3$) 2.54(m, 2H), 3.45(m, 2H), 3.57(s, 3H), 3.82(s, 3H), 4.20(m, 2H), 6.13(m, 1H), 6.90(d, J = 8.6 Hz, 2H), 7.31(d, J = 8.6 Hz, 2H), 8.15(d, J = 5.1 Hz, 1H), 8.84(d, J = 5.1 Hz, 1H), 9.26(s, 1H)	376
B026	($CDCl_3$) 2.60(m, 2H), 3.57-3.61(m, 5H), 3.78(s, 6H), 3.94(m, 2H), 5.76(m, 1H), 6.59(d, J = 8.5 Hz, 2H), 7.22-7.28(m, 2H), 8.20(d, J = 5.4 Hz, 1H), 8.84(d, J = 5.4 Hz, 1H), 9.27(s, 1H)	405(M+)
B027	($CDCl_3$) 2.54(m, 2H), 3.49(m, 2H), 3.55(s, 3H), 4.00(m, 2H), 5.83(m, 1H), 7.30(m, 1H), 7.43(m, 1H), 7.53(m, 1H), 7.69(d, J = 8.0 Hz, 1H), 8.14(m, 1H), 8.82(d, J = 5.1 Hz, 1H), 9.26(s, 1H)	413(M+)
B033	(d_6-DMSO) 2.48-2.50(m, 2H), 3.03(s, 3H), 3.41(m, 2H), 3.57(m, 2H), 5.90(m, 1H), 6.90(s, 1H), 7.19-7.25(m, 3H), 7.30-7.41(m, 6H), 8.09(dd, J = 1.4, 5.1 Hz, 1H), 9.00(d, J = 5.1 Hz, 1H), 9.28(d, J = 1.4 Hz, 1H)	421(M+)
B043	($CDCl_3$) 2.55(m, 2H), 3.45(m, 2H), 3.57(s, 3H), 4.22(m, 2H), 6.28(m, 1H), 7.17(m, 1H), 7.23(m, 1H), 7.30-7.34(m, 2H), 8.16(d, J = 5.4 Hz, 1H), 8.86(d, J = 5.4 Hz, 1H), 9.27(s, 1H)	351(M+)
B044	(d_6-DMSO) 2.48-2.50(m, 2H), 3.46-3.49(m, 5H), 4.26(m, 2H), 6.28(m, 1H), 6.98(s, 1H),	351(M+)

	7.06(dd, J = 3.4, 5.1 Hz, 1H), 7.21(d, J = 3.4 Hz, 1H), 7.43(d, J = 5.1 Hz, 1H), 8.27(d, J = 5.1 Hz, 1H), 9.00(d, J = 5.1 Hz, 1H), 9.29(s, 1H)	
B049	(d_6-DMSO) 2.69(m, 2H), 3.47(s, 3H), 3.57(m, 2H), 4.44(m, 1H), 6.99(s, 1H), 7.15(m, 1H), 7.45(m, 1H), 7.67(m, 1H), 7.80(d, J = 8.6 Hz, 1H), 8.17-8.22(m, 2H), 9.01(d, J = 5.1 Hz, 1H), 9.29(s, 1H)	387
B057	($CDCl_3$) 1.80-2.10(4H,m), 2.55-2.65(2H,m), 3.47(4H,dd,J=5.4,10.2Hz), 3.59(3H,m), 3.66(2H,t,J=6.9Hz), 4.25(2H,d,J=1.2Hz), 6.25-6.35(1H,m), 7.32(1H,s), 7.42(2H,d,J=8.4Hz), 7.55(2H,d,J=8.4Hz), 8.16(1H,dd,J=1.2,5.1Hz), 8.87(1H,d,J=5.1Hz), 9.28(1H,s)	443

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM ß-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ-^{32}P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25℃ for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter.

The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the A β neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 3

Compound No.	IC_{50} (nM)
A001	7
A002	1.2
A004	13
A012	17
A020	5
A022	8.7
A026	16
A027	31
A050	8
A056	27
A057	24

Compound No.	IC_{50} (nM)
B001	6.5
B002	1.1
B004	6.3
B005	0.38
B012	3.9
B017	5.6
B022	7.7
B026	2.4
B027	2.6
B033	17
B043	17
B044	9
B049	5.1
B057	6.8

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

Industrial Applicability

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as neurodegenerative diseases (e.g. Alzheimer disease) and the above-mentioned diseases.